Organization of oxidative phosphorylation supercomplexes in intact mitochondria

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Abstracts

S18 Mitochondrial Structure and Dynamics

Lectures

18L.1 Organization of oxidative phosphorylation supercomplexes in intact mitochondria

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The five complexes (complexes I–V) of the oxidative phosphorylation (OXPHOS) system of mitochondria are able to form specific supercomplexes. Structural characterization of these supercomplexes at low to medium resolution has been performed in two ways: (1) Single-particle electron microscopy. This technique has provided 2D and 3D data describing the interaction between complexes I + III, I + III + IV (respirasome) and in a dimeric form of complex V. (2) Electron tomography. Cryo-electron tomography (CET) is an emerging electron microscopic technique for reconstructing the 3D volume of large non-periodic objects, such as organelles, under cryogenic "life-like" conditions by incremental tilting the specimen. We have obtained 3D reconstructions (tomograms) by cryo-ET of intact mitochondria from several species. An advantage of cryo-ET is the possibility to average 3D subvolumes containing a specific type of particle. Averaging of subvolumes containing dimeric ATP synthase provided details at 5 nm resolution, the first insight into the arrangement a supercomplex with an intact mitochondrion.

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18L.2 Membrane traffic encounters mitochondria during cell death

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It is now established that mitochondria play a central role in all major pathways of cell death. The extrinsic pathway is the most physiological way of inducing cell death and uses surface receptors like Fas/CD95, which engage diverse cellular organelles including mitochondria. Recently, it has emerged that death signalling is linked to alterations in membrane traffic that involve endosomes and Golgi organelles merging with mitochondria, especially in the peri-nuclear region of cells. These alterations, collectively labelled 'organelle scrambling', occur before or immediately after the initial activation of caspases and may contribute to the release of apoptogenic factors like cytochrome *c* from mitochondria. How membrane organelles communicate with mitochondria is not well known, also because most scientists tend to focus on a single organelle at a time. Our recent studies on Fas-induced death unveil new forms of membrane interactions between mitochondria and other organelles that may help propagating death signalling within cells. These interactions suggest that mitochondria, contrary to what is often assumed, are on the receiving end of other organelles during death signalling. Whether mitochondria independently decide to kill the cell in which they thrive is thus an open question, which will be discussed in detail at the conference.

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18L.3 Bcl-2 Proteins regulate mitochondrial dynamics, energetics and neuronal activity

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Both anti- and pro-apoptotic Bcl-2 family proteins are important for development, for neuronal activity, and for mitochondrial dynamics. They are expressed in many adult tissues, but also are deregulated in many tumors. However, the conserved biochemical function that explains how the 3-dimensional structure shared by pro- and anti-apoptotic Bcl-2 family proteins functions to inhibit cell death remains a mystery. We have uncovered unexpected pro-survival functions of pro-apoptotic Bax, Bak and Bad in animals and in cultured cells (*Nat. Med.* 1999; *Dev. Cell.* 2003; *J. Biol. Chem.* 2004), and we have found novel activities and pro-death functions of the anti-apoptotic Bcl-2 and Bcl-xL proteins (*Nature* 1996; *Science* 1997; *J. Cell. Biol.* 2009). In search of the biochemical mechanisms to explain their normal cellular functions in healthy cells, we have studied Bcl-2 family proteins in regulating metabolism and mitochondrial membrane structure using several model systems including mammalian knockout mouse neurons and their mitochondria, synthetic lipid vesicles and yeast genetics. Exploration of knockout mice has uncovered a role of Bcl-xL in complex V, and yeast genetics studies has led us to a new model of human tumorigenesis.

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